Certificate of Mailing

Date of Deposit 6/21/00 Label Number: EL488649757US

I hereby certify under 37 CFR 1.10 that this correspondence is being deposited with the United States Postal Service as **"Express Mail Post Office to Addressee"** with sufficient postage on the date indicated above and is addressed to BOX PCT, Commissioner for Patents, Washington, D.C. 20231.

Elvis De La Cruz
Printed name of person mailing correspondence

Elvis De La Cruz
Signature of person mailing correspondence

Substitute Form PTO 1390 U.S. Department of Commerce Patent and Trademark Office TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	Attorney's Docket Number: 50124/005001 U.S. Application Number: Not Yet Assigned

INTERNATIONAL APPLICATION NUMBER	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/AU99/00062	29 January 1999	29 January 1998

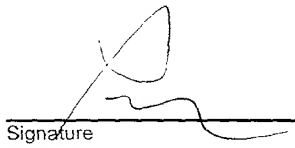
TITLE OF INVENTION:	THERAPEUTIC COMPOUNDS
APPLICANTS FOR DO/EO/US:	Roy W. Jackson, Kamani R. Subasinghe, and Alan L. A. Boura,

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1.	■ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2.	□ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3.	■ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4.	■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5.	A copy of the International Application as filed (35 U.S.C. 371(c)(2)). □ a. is transmitted herewith (required only if not transmitted by the International Bureau). ■ b. has been transmitted by the International Bureau. □ c. is not required, as the application was filed with the United States Receiving Office (RO/US).
6.	□ A translation of the International Application into English (35 U.S.C. 371(c)(2).
7.	Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)). □ a. are transmitted herewith (required only if not transmitted by the International Bureau). □ b. have been transmitted by the International Bureau. □ c. have not been made; however, the time limit for making such amendments has NOT expired. □ d. have not been made and will not be made.
8.	□ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9.	■ An oath or declaration of the inventors (35 U.S.C. 371(c)(4)).
10.	□ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5).
11.	□ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12.	□ An assignment for recording. A separate cover sheet in compliance with 37 3.28 and 3.31 is included.
13.	□ A FIRST preliminary amendment. □ A SECOND or SUBSEQUENT preliminary amendment.

14.	□ A substitute specification.				
15.	□ A change of power of attorney and/or address letter.				
16.	■ Other items or information: postcard				
17.	■ The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492(A)(1)-(5)): Neither international preliminary examination fee (37 CFR 1.482) nor international serach fee (37 CFR 1.455(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $ 970.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $ 840.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $ 690 00 International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1) - (4) $ 670.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) $ 96.00				
			ENTER APPROPRIATE BASIC FEE AMOUNT =	$970.00	
	Surcharge of $130 for furnishing the oath or declaration later than □ 20 OR □ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).			$0	
	CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
	Total claims	27 - 20 =	7	x $18.00	$126.00
	Independent claims	2 - 3 =	0	x $78.00	$0
	Multiple dependent claims (if applicable)			+ $260.00	$ 260.00
			TOTAL OF ABOVE CALCULATIONS =		$1356.00
	Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed with this request (Note 37 CFR 1.9, 1.27, 1.28).				$0
			SUBTOTAL =		$ 1356.00
	Processing fee of $130.00 for furnishing the English translation later than □ 20 OR □ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ 0
			TOTAL NATIONAL FEE =		$ 1356.00
	Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property. +				$ 0
			TOTAL FEES ENCLOSED =		$ 1356.00
				Amount to be refunded	$
				charged	$

■ a. A check in the amount of $ 1356.00 to cover the above fees is enclosed. □ b. Please charge my Deposit Account No. 03-2095 in the amount of $ [**.**] to cover the above fees. ■ c. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 03-2095.
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO: Paul T. Clark Clark & Elbing LLP 176 Federal Street Boston, MA 02110-2214 Telephone: 617-428-0200 Facsimile: 617-428-7045	 Signature Paul T. Clark Reg No. 30,162

\\Ntserver\documents\50124\50124.005001.U.S. National Appln Transmittal.wpd

ATTORNEY DOCKET NO. 50124/005001

Applicant or Patentee	: Roy W. Jackson et al.
Serial or Patent No.	: 09/582,059
Filed or Issued	: June 21, 2000
Title	: THERAPEUTIC COMPOUNDS

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) and 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am

[ ] the owner of the small business concern identified below:
[X] an official of the small business concern empowered to act on behalf of the concern identified below:

Name of Small Business Concern: Polychip Pharmaceuticals Pty Ltd.

Address of Small Business Concern: 10 WALLACE AVE, TOORAK VIC 3142 AUSTRALIA

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.12, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled THERAPEUTIC COMPOUNDS by inventors ROY W. JACKSON, KAMANI R. SUBASINGHE, AND ALAN L. A. BOURA described in

[ ] the specification filed herewith.
[X] application serial no. 09/582,059, filed June 21, 2000.
[ ] patent no. [**PATENT NUMBER**], issued [**ISSUE DATE**].

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d), or a nonprofit organization under 37 CFR 1.9(e). *NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

Assignee Name: Monash University

Assignee Address: WELLINGTON RD, CLAYTON VIC 3168

[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [✓] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent on which this verified statement is directed.

Name: C. BELYEA

Title: LICENSING AND PROJECTS MANAGER

Address: 10 WALLACE AVE, TOORAK VIC 3142 AUSTRALIA

Signature: C Belyea **Date:** 4 Oct 2000.

ATTORNEY DOCKET NO. 50124/005001

Applicant or Patentee : Roy W. Jackson et al.
Serial or Patent No. : 09/582,059
Filed or Issued : June 21, 2000
Title : THERAPEUTIC COMPOUNDS

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) and 1.27(d)) - NONPROFIT ORGANIZATION

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

Name of Organization: Monash University
Address of Organization: Dept. of Chemistry, PO Box 23, VICTORIA 3800, AUSTRALIA
Type of Organization:

[✓] University or Other Institution of Higher Education
[ ] Tax Exempt under Internal Revenue Service Code (26 USC 501(a) and 501(c)(3))
[ ] Nonprofit Scientific or Educational under Statute of State of the United States of America
Name of State:
Citation of Statute:
[ ] Would Qualify as Tax Exempt under Internal Revenue Service Code (26 Usc 501(a) and 501(c)(3)) If Located in the United States of America
[ ] Would Qualify as Nonprofit Scientific or Educational under Statute of State of the United States of America If Located in the United States of America
Name of State:
Citation of Statute:

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 37 CFR 1.9(e) for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code with regard to the invention entitled THERAPEUTIC COMPOUNDS by inventors ROY W. JACKSON, KAMANI R. SUBASINGHE, AND ALAN L. A. BOURA described in

[ ] the specification filed herewith.
[x] application serial no. 09/582,059, filed June 21, 2000.
[ ] patent no. [**PATENT NUMBER**], issued [**ISSUE DATE**].

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization with regard to the above identified invention.

If the rights held by the nonprofit organization are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(c) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

*NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

Full Name: Polychip Pharmaceuticals Pty Ltd.
Address:
[ ] INDIVIDUAL [✓] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Name:

Title:

Address:

Signature: _____ **Date:** 24/10/00

THERAPEUTIC COMPOUNDS

This invention relates to novel structural analogues and derivatives of compounds with general analgesic or related pharmacological activity. In particular the invention relates to derivatives of opioid compounds, particularly morphine and related compounds.

BACKGROUND OF THE INVENTION

A large range of therapeutic compounds is currently used in the treatment of conditions such as allergies, diarrhoea, migraine and other pain conditions, and in the treatment of congestive heart failure. These compounds include compounds with analgesic or related activities, such as anti-tussives, anti-depressants, local anaesthetics, anti-hypertensives, anti-asthmatics, anti-histamines, and anti-serotonins.

However, many of the therapeutic compounds of the types enumerated above have undesirable side-effects, such as the respiratory depression caused by opiates. In particular, many drugs which are useful for their action on the peripheral nervous system have undesirable effects in the central nervous system.

Thus opiates are the most powerful analgesics known, but their usefulness is greatly limited by their side-effects, including severe respiratory depression, and ability to induce addiction and physical dependence.

Despite intensive efforts to design analogues of morphine and related opioids which retain the analgesic activity but which do not have a deleterious effect on the central nervous system and the bowel, success has been limited. Structure-activity relationships have been extensively investigated, and a number of features have been widely accepted as essential. See for example "An Introduction to Pharmacology" by J.J. Lewis (E. & S. Livingston Ltd, 1964 Pages 401-407), and "Principles of Drug Action: The Basis of Pharmacology (Ed. W.B. Pratt and

P.Taylor; Churchill Livingstone, 3rd edition, 1990, Pages 25-27). In particular, it is generally considered that to retain analgesic activity the group on the tertiary nitrogen should be small, and should preferably be methyl; larger substituents are likely to be opiate receptor antagonists rather than agonists. Thus replacement of the methyl group of morphine by an allyl or cyclopropylmethyl moiety produces an antagonist. Although there are some exceptions to this rule, such as N-amylnormorphine and N-hexylnormorphine, in general a large substituent will result in antagonist activity.

We have attempted to modify the ability of biologically-active compounds to cross the blood-brain barrier by incorporating a highly polar group into the molecular structure. Thus we have shown that derivatives of the 2N atom of mianserin comprising a guanidino group show H_1 and 5-hydroxytryptamine activity, but show no detectable activity in the central nervous system. In contrast, a compound in which the 2N atom of mianserin was substituted with a urea group still showed pronounced central nervous system activity (Jackson *et al*; Clin. Ex. Pharmacol. Physiol., 1992 19 17-23 and our U.S. Patent No. 5,049,637).

Naltrexamine and oximorphamine have been modified by incorporation of groups which are zwitterionic at biological pH in order to restrict access to the central nervous system (Botros *et al*; J. Med. Chem., 1989 32 2068-2071, and Portoghese, U.S. Patent No. 4,730,048). In US-4,730,048 the zwitterionic group was added at C6. Some of these analogues were full agonists, and one was a strong antagonist.

A bis(t-butyldimethylsiloxy)-substituted compound in which a guanidino derivative was attached to the nitrogen via a 3 carbon spacer chain was found to show no opioid activity at μ-receptors in isolated guinea-pig ileum (Jackson *et al*, 1992). This suggested that such compounds would not have the desired activity.

Therefore there is a need for therapeutic compounds which have less activity within the central nervous system, thus having fewer undesirable side-effects, whilst at the same time having greater specificity of action on peripheral physiological mechanism. We have found that several compounds with the general formula outlined below not only have reduced central side-effects, but retain activity at desired peripheral receptors. In particular, those compounds which show activities at opioid receptors retain broad analgesic activity, contrary to current orthodoxy which teaches that the analgesic effects of opioids are mediated from the CNS. Their selectivity for peripheral opioid receptors not only makes them useful for the treatment of pain without sedative or addictive effects, but also may make them useful for treatment of AIDS and related immune deficiency diseases.

SUMMARY OF THE INVENTION

In its broadest aspect, the invention provides an opioid compound of general formula I

[opioid-N]-[spacer]-[charged group],

I

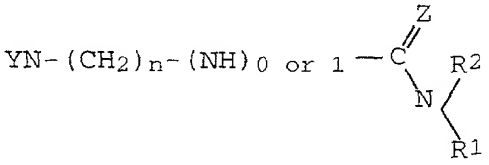
in which an opioid compound is linked via the nitrogen at position 17 to a spacer group, which in turn is linked to a charged group.

For the purposes of this specification, the term "opioid compound" is to be taken to mean a compound structurally related to morphine. The opioid compound preferably, but not necessarily, has opioid agonist or antagonist activity at opioid receptors.

The spacer can be any spacer group of dimensions approximately equivalent to an alkyl chain of 1 to 6 carbon atoms, and may for example be a straight or branched alkyl, alkenyl or alkenyl chain of 1 to 6 carbon atoms, which may

optionally be substituted. The spacer may also comprise a cyclic alkyl, alkenyl or alkynyl group. Preferably the spacer group is unsubstituted, and more preferably is of 2 to 3 carbon atoms. The charged group may be any group which has the ability to restrict access of the compound of formula I to the central nervous system, and is preferably an amidine or guanidine group.

According to one embodiment, the present invention provides an opioid compound of general formula (II)



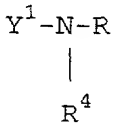
in which

YN- represents an organic residue obtained by removal of the R group from an opioid compound of general formula

YN-R (IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

or of the general formula

 (IIIb)

wherein R^4 is methyl or ethyl, and

Y^1-NR^4 represents the corresponding organic residue;

Z is O, S or NR^3;

R^1 is H_1, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen,

or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

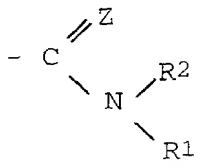
R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

n is an integer of 1 to 6,

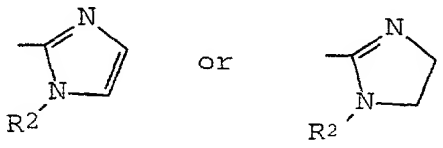
and wherein

R^1 and R^3 may together complete an addition ring;

then the grouping



may become a heterocyclic moiety such as 2-imidazolyl or 2-imidazolinyl:



Preferably R is CH_3.

Preferably n is 2 or 3.

Preferably Z is NH, and R^1 and R^2 are both H.

In order to indicate the trivalent N-atom more clearly, the structure of compounds of the formula (IIIa) may be written

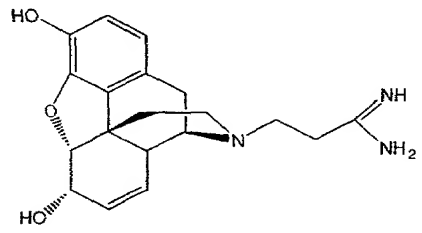
(IIIc)

The precursors of YN- and Y^1NR^4- respectively are selected from compounds which are structurally related to morphine.

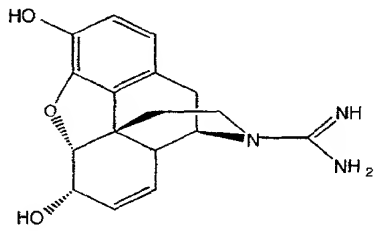
Thus the precursor of YN- or Y^1NR^4- is preferably a compound selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, etorphine, acetorphine, ketobemidone, ethoheptazine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine and metazocine.

Preferably the precursor is morphine, codeine or buprenorphine.

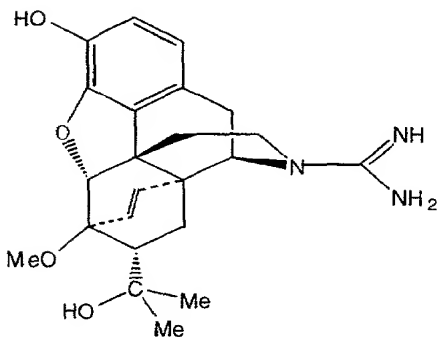
In a preferred embodiment, the compound of general formula I is one of the following:



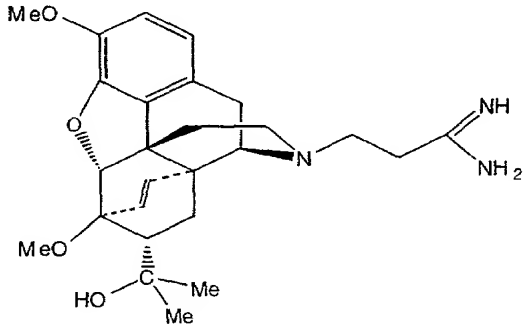
KRS-41



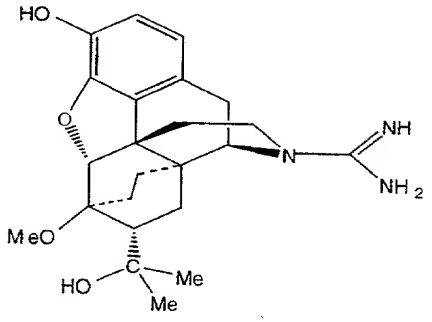
KRS-2-19



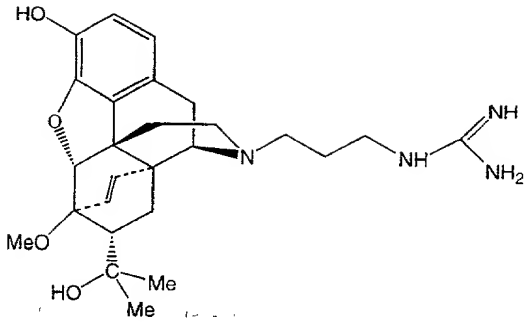
KRS-3-23-4



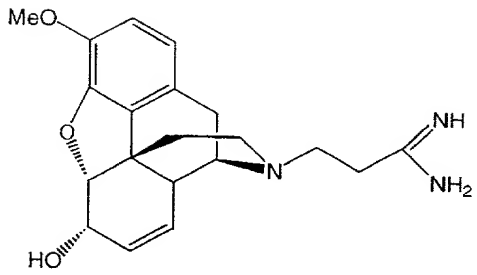
KRS-3-28



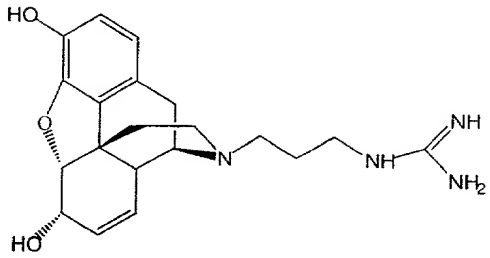
KRS-3-30-2



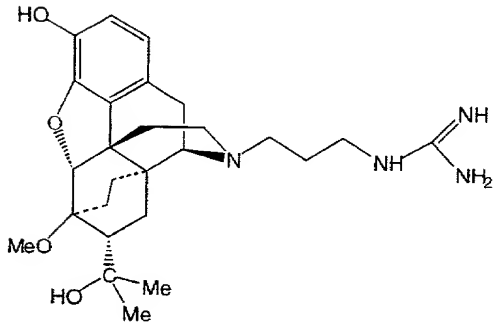
KRS-3-56



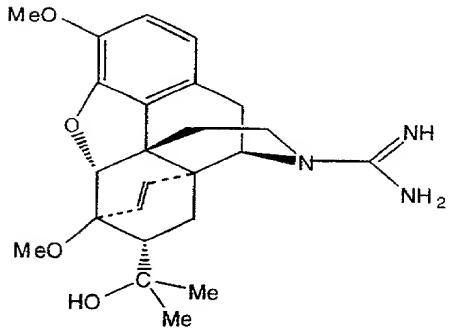
KRS-2-63



KRS-2-47



KRS-4-8



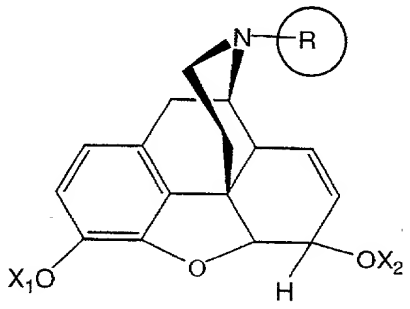
KRS-3-7

Typical examples of morphine-related compounds of the formula (IIIa) or (IIIc) are illustrated in Table 1. In each case the group R has been circled in order to clearly identify the residue YN- or Y^1NR^4- as the remainder of the molecule.

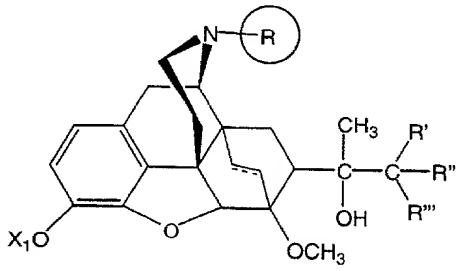
The preferred precursors also include the unnamed compounds whose structures are shown in Table 1, with the nitrogen atom at position 17 indicated.

Table 1

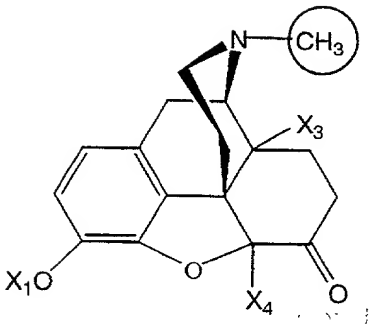
Compounds with Analgesic or Related Type Activity and Some Related Structures



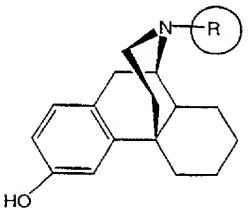
R	X_1	X_2	Name
CH_3	H	H	Morphine
"	CH_3	H	Codeine
"	Et	H	Ethylmorphine
"	Ac	Ac	Heroin
"	CH_2COOH	H	O-Carboxymethylmorphine
"	Ac	H	O-Acetylmorphine
"	$tBuMe_2Si$	$tBuMe_2Si$	"Disilyl" morphine
H	$tBuMe_2Si$	$tBuMe_2Si$	"Disilyl" normorphine



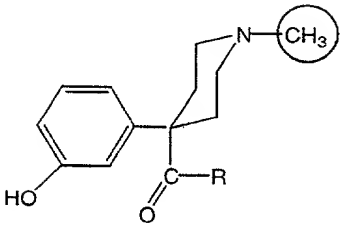
R	X	- or =	R'	R''	R'''	Name
CH_3	H	=	H	H	Et	Etorphine
"	Ac	=	H	H	Et	Acetorphine
"	H	-	H	H	Et	-
"	Ac	-	H	H	Et	-
CH_2-◁	H	=	H	H	H	Diprenorphine
"	H	=	CH_3	CH_3	CH_3	Buprenorphine



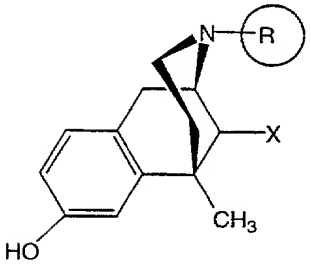
X_1	X_3	X_4	Name
CH_3	H	H	Hydrocodone
H	H	H	Hydromorphone
H	OH	H	Oxymorphone
CH_3	OH	H	Oxycodone
H	H	CH_3	Metopon



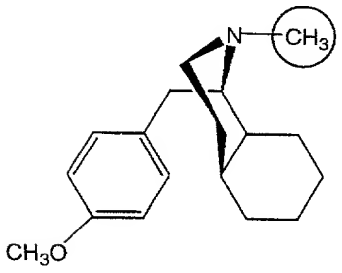
R	Name
$PhCH_2CH_2$	Phenomorphan
CH_3	Levorphanol



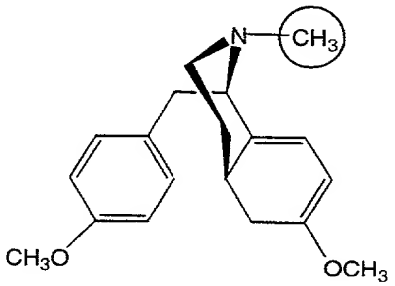
R	Name
CH_3CH_2	Ketobemidone
CH_3CH_2O	Ethoheptazine



R	X	Name
CH_3	CH_3	Ketobemidone
H	CH_3	Eptazocine
$Me_2C=CHCH_2-$	CH_3	Pentazocine



Dihydrocodeine



Thebaine

Thus the invention provides in a second broad aspect an opiate receptor agonist having analgesic properties and having reduced or no CNS activity. Preferably the opiate receptor agonist is a compound of general formula I or general formula II as defined above.

Where appropriate, the invention also includes pharmaceutically acceptable salts of the compounds of formula I, or formula II. A variety of pharmaceutically-acceptable salt-forming organic and inorganic acids is well known in the art.

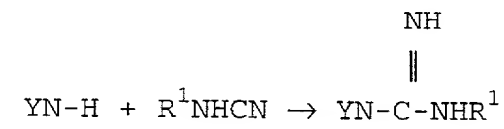
According to third aspect, the invention provides a method of reducing the central nervous system activity of an opioid compound, comprising the step of linking the nitrogen atom at position 17 of said compound to a spacer group, which in turn is linked to a charged group. Optionally the linkage to the charged group is via a spacer group.

According to a fourth aspect of the invention, methods for the preparation of the compounds of formula II are provided, as set out below, in which it will be appreciated that YN- may be replaced by Y^1NR^4-:

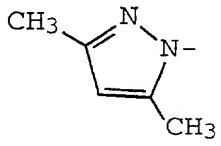
1. By the reaction of a compound of formula

(IV)

with a cyanamide, R^1NHCN, according to the equation

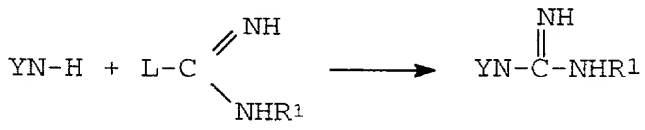


wherein L is a suitable leaving group, for example CH_3O, CH_3S, CH_3SO_2, SO_3H or



(3,5-dimethylpyrazol-1-yl)

according to the equation

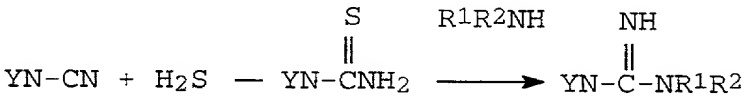


Compounds of the formula (II) wherein Z is S not only possess useful therapeutic activity *per se*, but may also be used as intermediates for the preparation of compounds of formula II wherein Z is NR^2, *eg.*

3. By the reaction of a compound of the formula

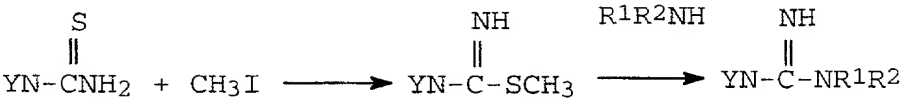
$$YN\text{-}CN \qquad (VI)$$

with H_2S there is obtained an N-thiocarboxamide $YN\text{-}CSNH_2$, which may be reacted with an amine R^1R^2NH according to the two-stage equation

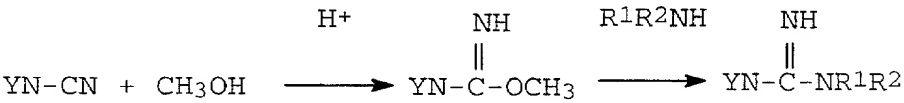


to yield compounds of the invention where Z is S and where Z is NH.

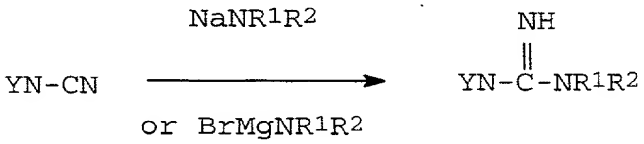
4. The N-thiocarboxamide may also be methylated, for example using CH_3I, to yield an isothiourea compound, which in turn may be reacted with an amine R^1R^2NH to yield a compound of the invention:



5. An alternative method of synthesis of compounds of formula (II) comprises reacting an N-cyano compound of formula (VI) with methanol under acidic conditions to yield an isourea, which in turn is reacted with an amine according to the equation



6. Compounds according to formula (II) where Z is N may also be prepared, for example from the N-cyano compound of formula (VI) and the appropriate metallated residue (for example, sodamide or metallated amines):



7. Compounds of the formula (VI), most of which are also novel, and which are useful as intermediates in reactions 3, 5 and 6 above, are prepared by reacting a compound of formula (III) (see Table 1) with cyanogen bromide in a hydrocarbon solvent:

$$YN\text{-}R + BrCN \rightarrow YN\text{-}CN$$

8. Compounds of general formula (IV), which are useful as intermediates in reactions 1 and 2, are prepared from the compounds of formula (III) (Table 1) by the following reactions:

$$YN\text{-}R + Cl_3CCH_2OCOCl \rightarrow YN\text{-}CO.OCH_2CCl_3$$

$$YN\text{-}COOCH_2CCl_3 \xrightarrow{Zn/AcOH} YN\text{-}H$$

Some compounds of the invention are optically active, and it will be clearly understood that both racemic mixtures and isolated stereoisomers are within the scope of the invention.

According to a fifth aspect, the invention provides a composition comprising as an effective agent a compound according to formula I, together with a pharmaceutically acceptable carrier.

Methods and pharmaceutical carriers for preparation of pharmaceutical compositions are well known in the art, as set out in textbooks such as Remington's Pharmaceutical Sciences, 17th Edition, Mack Publishing Company, Easton, Pennsylvania, USA.

According to a sixth aspect, the invention provides a method of inducing analgesia, comprising the step of administering an effective amount of a compound of the invention to a mammal in need of such treatment. The mammal may be a human, or may be a domestic, companion or zoo mammal. Preferably the mammal is a human.

The dosage to be used will depend on the nature and severity of the condition to be treated, and will be at the discretion of the attending physician or veterinarian. The most suitable dosage for a specific condition can be determined using normal chemical trial procedures.

For the purposes of this specification it will be clearly understood that the word "comprising" means "including but not limited to", and that the word "comprises" has a corresponding meaning.

Brief Description of the Figures

Figure 1 shows dose-response curves for morphine-like activity in guinea-pig stimulated ileum preparations, using morphine as standard:

a) Compounds KRS-3-28 and KRS-3-30-2 (4 animals in each group);

b) Compounds KRS-41 and KRS-2-19.

c) Compound KRS-3-56 (3 animals in each group).

DETAILED DESCRIPTION OF THE INVENTION

The invention will now be described in detail by way of reference only to the following non-limiting examples, and to the Figures.

Example 1 Preparation of N-Cyano Compounds, YN-CN

A solution of YN-R (0.02 mole of the base) in anhydrous benzene (20 ml) was added slowly to a stirred solution of cyanogen bromide (2.3 g) in anhydrous benzene (20 ml) in an atmosphere of nitrogen. After 24 hours, the mixture was diluted with diethyl ether (50 ml) and shaken with water (50 ml). The separated aqueous layer was back extracted with a mixture of benzene and ether (equal volumes of each, total 50 ml) and the combined organic layers dried over anhydrous potassium carbonate and then evaporated under reduced pressure. The residual solid was recrystallized from ethanol to give the N-cyano derivative YN-CN as colourless needles.

Example 2 Preparation of Carboxamidines, $YN-\overset{\overset{NH}{\|}}{C}-NH_2$

A solution of sodamide in liquid ammonia was prepared in the usual way from metallic sodium (0.35 g) in dried liquid ammonia (150 ml) in the presence of a trace of ferric nitrate. The reaction mixture was kept at about -70°C and moisture was rigorously excluded. The N-cyano derivative YN-CN (0.01 mol) was then added slowly, and the mixture stirred whilst dried hexamethylphosphorictriamide (HMPA) was added dropwise until the N-cyano compound began to dissolve; about 1 ml of HMPA was required. A deep brown solution was formed. The stirring was continued for 30 minutes and the solution poured cautiously into a solution of ammonium chloride (4 g) in iced water (150 ml). The resulting suspension was kept for some 30 minutes at

room temperature and the solid then filtered off and washed with a little water. The residue (a) was reserved. The combined filtrate and washings were concentrated *in vacuo* to about 25 ml, when a second crop of solid (b) separated. The two crops (a) and (b) were combined and recrystallized from isopropanol to give the carboxyamidine hydrochloride

$YN-C-NH_2.HCl$ as the colourless solid.

Example 3 Preparation of Thiocarboxamido Derivatives, $YN-CSNH_2$

Dry hydrogen sulphide was passed through a solution of the N-cyano compound YN-CN (500 mg) in a mixture of triethylamine (0.25 ml) and pyridine (25 ml) for 24 hours. The resulting solution was poured into water (150 ml) and the mixture stirred for 30 minutes at room temperature to afford colourless crystals which were filtered off, washed with fresh water and dried in *in vacuo*. Recrystallization from a mixture of diethyl ether and light petroleum gave colourless needles of the desired compound.

Example 4 Preparation of Carboxoamido Derivatives, $YN-CONH_2$

A slurry of the N-cyano compound YN-CN (0.02 moles) in aqueous hydrogen peroxide (100 Vol., 0.51 ml) and 20% aqueous sodium hydroxide (0.51 ml) was stirred for 30 minutes, during which time the reaction mixture became warm, then cooled to room temperature; some oxygen was evolved. Three portions of methanol (3 x 2 ml) were added to the reaction mixture, at 30 minute intervals with stirring. The mixture was warmed to 60°C for 15 minutes, then poured into water (50 ml) to give a white precipitate which was filtered at the pump, washed with water (2 x 10 ml) and dried *in vacuo* to give the N-carboxamido derivative $YN-CONH_2$ as a colourless solid.

Example 5 Preparation of 3,6-bis(t-butyldimethylsiloxy)-7,8-didehydro-4,5-epoxymorphinan (3,6α-Bis[dimethyl(1,1-dimethylethyl)siloxy]-7,8-didehydro-4,5α-epoxymorphinan)

Dry, alcohol-free dichloromethane (100 ml) was added to a flask containing normorphine (5.42 g, 20 mmol), *t*-butyldimethylsilyl chloride (6.62 g, 44 mmol), imidazole (6.12 g, 90 mmol), and 4-dimethylaminopyridine (120 mg, 1.0 mmol). After 20 hours of stirring at room temperature, the reaction mixture was diluted with ether (200 ml), washed with water (3 x 200 ml), dried (Na_2SO_4), and evaporated to give a grey-yellow solid (10.11 g). Recrystallization from ethanol gave very fine grey needles (5.20 g, 52%), m.p. 105.7-107.0°C. The mother liquors were recrystallized (ethanol, twice) to give a second crop (2.45 g, 25%), m.p. 105.0-106.7°C. A small portion of the first crop was recrystallized again to give m.p. 106.2-107.2°C.

Example 6 Preparation of 3,6-bis(t-butyldimethylsiloxy)-7,8-didehydro-4,5-epoxy-17-methylmorphinan (O,O'-Bis-t-butyldimethylsilyl-morphine)

Ref: Neuvo, J. Chim. 1980 4 (6) 369-375

Solid t-butylchlorodimethylsilane (3.8 g, 25 mmol) was added to a stirred solution of morphine (3.0 g, 10.5 mmol) and imidazole (3.6 g, 52.9 mmol) in dimethylformamide (DMF; 20 ml) under a nitrogen atmosphere. Stirring of the reaction mixture was continued at room temperature for 2 hours, then the mixture was heated to 90° for 4 hours. The mixture was poured into water (25 ml) then extracted into dichloromethane (3 x 25 ml), dried (K_2CO_3) and evaporated to give a yellow oil, which crystallised on addition of a small amount of methanol. Recrystallisation from methanol gave colourless needles m.p. 118-119°C (Lit 119-119.5°C) (5.02 g, 93%).

Example 7 Preparation of 3,6-bis(t-butyldimethyl-siloxy)-7,8-didehydro-4,5-epoxy-17-N-cyano-morphinan

A solution of bis-silylmorphine (7.0 g, 1.36 mmol) in dry benzene (50 ml) was added dropwise to a stirred solution of cyanogen bromide (2.9 g, 27.4 mmol) in dry benzene under a nitrogen atmosphere. The stirred solution was refluxed for 4 hours, allowed to cool to room temperature, then evaporated. The solid residue was purified by rotary chromatography (SiO_2: 5% ethanol in chloroform), then crystallisation from methanol to give 3,6-bis(t-butyldimethyl-siloxy)-7,8-didehydro-4,5-epoxy-17-N-cyano-morphinan (6.3 g, 86%).

Example 8 Preparation of O,O'-bis-t-butyldimethylsilyl-N-thiocarboxamidonormorphine

Cyanamide (524 mg, 1.0 mmol) and triethylamine (101 mg, 1.0 mmol) were dissolved in dry pyridine (20 ml). Dry hydrogen sulphide gas was slowly bubbled through the stirred pyridine solution for 4 hours, then the mixture was poured into water (100 ml), extracted into dichloromethane (3 x 20 ml), washed with water (3 x 20 ml), dried with $MgSO_4$, and evaporated. Recrystallisation from methanol gave colourless needles of the required O,O'-bis-t-butyldimethylsilyl-N-thiocarboxamidonormorphine (490 mg, 88%).

Example 9 Preparation of 3,6-bis(t-butyldimethyl-siloxy)-7,8-didehydro-4,5-epoxy-17-(N-carboxamidino)-morphinan

Ref: Ravi S. Garigipati, Tetrahedron Letters, Vol 31, No 14, pp 1969-1972, 1990.

J. I. Levin, E. Turos and S.M. Weinrub, Synthetic Communications, 12, 989-993, 1982.

A solution of 3,6-bis(t-butyldimethylsiloxy)-7,8-didehydro-4,5-epoxy-17-N-cyano-morphinan (100 mg.

0.19 mmol) in dry benzene (2 ml) was added to a solution of methylchloroaluminium amide (prepared according to the Weinrub procedure) in benzene at room temperature. This solution was heated at 80°C under nitrogen for 20 h. The reaction mixture was cooled, and the aluminium complex was decomposed by carefully pouring the solution into a slurry of silica gel (2.0 g) in chloroform. The mixture was stirred for 5 min and filtered. The filter cake was washed with methanol (50 mL). Evaporation of the filtrate gave a white solid (0.106 g), which was used in the next step without further purification.

Example 10 Preparation of (5α,6α)-7,8-didehydro-4,5-epoxy-17-N-(2-carboxamidino)-morphinan-3,6,-diol. (KRS-2-19)

Ref: R. Newton, D.Reynolds, M. Finch, D. Kelly, S. Roberts, Tetrahedron Letters, No 41, 3981-82, 1979.

A slurry of 3,6-bis(t-butyldimethylsiloxy)-7,8-didehydro-4,5-epoxy-17-(N-carboxamidino-morphinan (106 mg, 0.19 mmol) in 10:1 mixture of acetonitrile and tetrahydrofuran was cooled in an ice bath, and 40% aqueous HF (0.2 mL) was added dropwise. After stirring overnight at room temperature the reaction mixture was concentrated under reduced pressure to give a light yellow solid, which was passed through a short silica gel column using methylene chloride/methanol in 8:2 ratio as the eluent to give KRS-2-19 as a white solid (0.64 g, 98%).

Example 11 Alternative Preparation of 3,6-bis(t-butyldimethylsiloxy)-7,8-didehydro-4,5-epoxymorphinan

Normorphine, prepared according to Chemical Abstracts, Vol. 54, 162f, (100 mg, 0.36 mmol) was dissolved in dry DMF (0.5 mL) and imidazole (0.0628 g, 0.92 mmol) and dimethylaminopyridine (0.07 g) was added. t-Butyldimethyl-silyl chloride was then added in small amounts at room

temperature. After the addition was complete the reaction mixture was stirred at room temperature under nitrogen while being monitored by thin layer chromatography. After 10-15 min distilled water was added and the reaction mixture was extracted with methylene chloride. The methylene chloride layer was dried over potassium carbonate and evaporated under reduced pressure to give crude product, which was purified by column chromatography on silica gel using methylene chloride/methanol/ammonium hydroxide in 9:1:0.1 ratio as the eluent. (Yield = 120 mg, 65%).

Example 12 Preparation of 3,6-bis(t-butyldimethylsiloxy)-7,8-didehydro-4,5-epoxy-17-(N-2-cyanoethyl)morphinan

Ref: J.A.Bell and C. Kenworthy, Synthesis, 650-652, 1971.

3,6-Bis(t-butyldimethylsiloxy)-7,8-didehydro-4,5-epoxymorphinan (0.26 g, 0.52 mmol) was dissolved in absolute ethanol (3 mL) and acrylonitrile (0.07 ml, 1.0 mmol) was added dropwise at room temperature. The reaction mixture was stirred at room temperature overnight, and the solvent was evaporated under reduced pressure to give a white solid (0.26 g, 90% yield).

Example 13 Preparation of 3,6,bis(t-butyldimethylsiloxy)-7,8-didehydro-4,5-epoxy-17-N-[(2-aminoiminomethyl)ethyl]morphinan

A solution of 3,6-bis(t-butyldimethylsiloxy)-7,8-didehydro-4,5-epoxy-17-(N-2-cyanoethyl) morphinan (0.257 g, 0.46 mmol) in dry benzene (5 mL) was added to a solution of methylchloroaluminum amide in benzene at room temperature. The solution was heated at 80°C under nitrogen for 20 h. This was worked up as before to give a white solid (0.157 g), which was used for the next step without further purification.

Example 14 Preparation of (5α,6α)-7,8-didehydro-4,5-epoxy-17-N-[(2-aminoiminomethyl)ethyl]-morphinan-3,6-diol. (KRS-41)

The crude 3,6,bis(t-butyldimethylsiloxy)-7,8-didehydro-4,5-epoxy-17-N[(2-aminoiminomethyl)ethyl]-morphinan was deprotected using 40% HF in 10:1 mixture of acetonitrile and tetrahydrofuran as described before. The product was triturated with ethylacetate and with methanol. The remaining white precipitate was recrystallized with ethanol and water to give KRS-41 as a white powder (90 mg) in 94% yield.

Example 15 Preparation of N-carboxamidino-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydro-northebaine (KRS-3-7)

N-Cyano-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronorthebaine was prepared according to the method of Bentley and Hardy, J. Amer. Chem. Soc., 1967 89 3281-3292. This compound was reacted with methylchloroaluminum amide in benzene as described before. The crude product was purified by column chromatography on silica gel using methylene chloride/methanol/ammonium chloride in 6:1:0.1 ratio as the eluent to give KRS-3-7 as a white solid (56 mg. 91% yield).

Example 16 Preparation of N[(2-aminoiminomethyl)ethyl]-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronorthebaine (KRS-3-28)

7α-(1-Hydroxy-1-methylethyl)6,14-endo-ethenotetrahydronorthebaine, prepared according to the method of Bentley and Hardy (1967) *op. cit.*, was converted to the corresponding N-2-cyanoethyl compound in 96% yield by reacting with acrylonitrile in absolute ethanol.

N-2-Cyanoethyl-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronorthebaine was then reacted with methylchloroaluminum amide in benzene as described above. The crude product was purified by column chromatography on

silica gel using methylene chloride/methanol/ammonium chloride in 9:1:0.1 ratio as the eluting solvent to give KRS-3-28 (125 mg, 45 % yield).

Example 17 N-Carboxamidino-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydro-nororipavine (KRS-3-23-4)

3-O-Acetyl-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydrooripavine, prepared according to the method of Bentley and Hardy, *op.cit.*, was reacted with cyanogen bromide in dry methylene chloride to give 3-O-acetyl-N-cyano-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronororipavine in 97% yield. This compound was then reacted with methylchloroaluminum amide in benzene as described above. The crude product was purified by column chromatography on silica gel using methylene chloride/methanol/ammonium chloride in 6:1:0.1 ratio as the eluting solvent to give KRS-3-23-4 as a white solid (102 g, 34% yield).

Example 18 N-Carboxamidino-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethanotetrahydro-oripavine (KRS-3-30-2)

7α-(1-Hydroxy-1-methylethyl)-6,14-endo-ethanotetrahydro-oripavine was prepared by the method of Lewis, J.W., "Narcotic Antagonists", in Advances in Biochemical Psychopharmacology, 1974 8 123-136, Raven Press, New York. The 3-O-acetyl ester was prepared by the addition of acetic anhydride to a solution of the phenol in aqueous sodium hydroxide, and was obtained as a white solid. The O-acetyl ester was then reacted with cyanogen bromide in dry chloroform to give N-cyano-nororipavine derivative in 70% yield, which was then reacted with methychloroaluminum amide in benzene. The crude product was purified by column chromatography on silica gel using methylene chloride/methanol/ammonium hydroxide in 9:1:0.1

ratio. KRS-3-30-2 was obtained as a white powder in 30% yield.

Example 19 N-(N'-carboxamidino-3-aminopropyl)-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronororipavine (KRS 3-56)

a) Preparation of N-2-cyanoethyl-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronororipavine

7α-(1-Hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronororipavine was prepared according to the method of K.W. Bentley and D.G. Hardy, Journal of the American Chemical Society, 1967 89 3281-3292. This compound was reacted with acrylonitrile in absolute ethanol as described. The crude product was purified by column chromatography on silica gel using methylene chloride/ethyl acetate/methanol in 4:4:1 ratio as the eluent.

b) Preparation of 3-(t-butyldimethylsiloxy)-N-2-cyanoethyl-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydro-nororipavine

Solid t-butyldimethylsilyl chloride (0.035 g, 0.227 mmol) was added in small amounts to a stirred solution of N-2-cyanoethyl-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronororipavine (80 mg, 0.189 mmol), imidazole (0.015 g, 0.227 mmol) and 4-dimethylaminopyridine (0.005 g) in anhydrous dimethylformamide (0.5 ml) under a nitrogen atmosphere. After stirring for 1h at room temperature distilled water (10 ml) was added to the reaction mixture and the mixture was extracted with methylene chloride. The organic layer was dried over potassium carbonate and evaporated under reduced pressure. The solid formed was purified by column chromatography on silica gel, using ethyl acetate/X4 in 1:1 ratio as the eluent. (Yield = 79 mg, 78%)

c) Preparation of 3-(t-butyldimethylsiloxy)-N-(3-aminopropyl)-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydro-nororipavine.

3-(t-butyldimethylsiloxy)-N-2-cyanoethyl-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydro-nororipavine (100 mg, 0.186 mmol) in dry ethyl ether (2 ml) was added dropwise to lithium aluminium hydride (0.008 g, 0.223 mmol) in dry ether (2 ml). After stirring for 3 h at room temperature wet ether followed by 10% NaOH (1 ml) was added to the reaction mixture. The solution was filtered and the white precipitate was washed with ether. The ether layer was evaporated under reduced pressure to give the amine as a white solid (99 mg, 98%).

d) Preparation of 3-(t-butyldimethylsiloxy)-N-(N-carboxamidino-3-aminopropyl)-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronororipavine

Ref: Michael S. Bernatowicz, Youling Wu and Gary R. Matsueda, Journal of Organic Chemistry, 1992 57 2497-2502

To a mixture of 3-(t-butyldimethylsiloxy)-N-(3-aminopropyl)-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronororipavine (0.196 g, 0.37 mmol), diisopropylethylamine (0.065 ml, 0.37 mmol) and 1H-pyrazole-1-carboxamidine hydrochloride (0.055 g, 0.37 mmol) was added anhydrous dimethylformamide (2 ml), and the reaction mixture was stirred at room temperature under nitrogen for overnight. The reaction mixture was evaporated to dryness under reduced pressure, and the crude product was chromatographed on silica gel.
(Yield = 0.191 g, 88%).

e) Preparation of N-(N'-carboxamidino-3-aminopropyl)-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydro-nororipavine (KRS 3-56)

40% HF (0.3 ml, 0.0065 mol) was added dropwise to 3-(t-butyldimethylsiloxy)-N-(N'-aminoiminomethyl-

aminopropyl)-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethenotetrahydronororipavine (0.191 g, 0.3 mmol) in 10:1 mixture of acetonitrile/tetrahydrofuran (10 ml), and the reaction mixture was stirred overnight at room temperature. The white precipitate formed was filtered and was washed with acetonitrile and then with methanol to give KRS 3-56 as a white solid (0.135 g, 96%).

Example 20 5α,6α-7,8-didehydro-4,5-epoxy-3-methoxy-17-N-[(2-aminoiminomethyl)ethyl]morphinan (KRS-2-63)

a) Preparation of 7,8-didehydro-4,5-epoxy-17-(N-2-cyanoethyl)morphinan-3,6-diol

Acrylonitrile (0.03 mL, 0.44 mmol) was added dropwise to normorphine (0.1 g, 0.37 mmol) in absolute ethanol (2 mL) at room temperature. The reaction mixture was stirred at room temperature overnight and the solvent was evaporated under reduced pressure. The crude product was chromatographed on silica gel using ethylacetate and hexane in 3:1 ratio as the eluent (yield = 86 mg, 71%).

b) Preparation of 7,8-didehydro-4,5-epoxy-3-methoxy-17-(N-2-cyanoethyl)morphinan-6-ol

7,8,-Didehydro-4,5-epoxy-17-(N-2-cyanoethyl)-morphinan-3,6-diol (86 mg, 0.265 mmol) was suspended in dry acetone (2 mL), and anhydrous potassium carbonate (0.037 g, 0.27 mmol) was added, followed by methyl iodide (0.025 ml, 0.39 mmol). After refluxing for 5 h the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel using ethylacetate and hexane in 2:1 ratio as the eluting solvent (yield = 70 mg, 78%).

c) Preparation of 6-t-butyldimethylsiloxy-7,8-didehydro-4,5-epoxy-3-methoxy-17-(N-2-cyanoethyl)morphinan

7,8-Didehydro-4,5-epoxy-3-methoxy-17-(N-2-cyanoethyl)morphinan-6-ol (50 mg, 0.15 mmol) was dissolved

in dry dimethylformamide (0.5 mL), and imidazole (11.1 mg, 0.16 mmol) and dimethylaminopyridine (20 mg) was added. t-Butyldimethylsilyl chloride (24.1 mg, 0.16 mmol) was then added at room temperature under nitrogen atmosphere. After stirring for 2 h at room temperature, distilled water was added and the reaction mixture was extracted with methylene chloride. The methylene chloride layer was dried with potassium carbonate and evaporated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel using ethylacetate/hexane in 3:1 ratio as the eluent (yield = 50 mg, 73%).

d) Preparation of 6-t-butyldimethylsiloxy-7,8-didehydro-4,5-epoxy-3-methoxy-17-N-[(2-aminoiminomethyl)ethyl]-morphinan

A solution of 6-t-butyldimethylsiloxy-7,8-didehydro-4,5-epoxy-3-methoxy-17-(N-2-cyanoethyl)morphinan (50 mg, 0.11 mmol) in dry benzene (2 mL) was added to a solution of methylchloroaluminum amide in benzene at room temperature. The solution was heated at 80°C under nitrogen for 20 h. The reaction mixture was worked up as before to give a light brown solid, which was purified by column chromatography on silica gel using methylene chloride/methanol/ammonia in 9:1:0.1 ratio to give the product as a white solid (yield = 44 mg, 85%).

e) Preparation of 5α,6α-7,8-didehydro-4,5-epoxy-3-methoxy-17-N-[(2-aminoiminomethyl)ethyl]morphinan (KRS-2-63)

6-t-Butyldimethylsiloxy-7,8-didehydro-4,5-epoxy-3-methoxy-17-N-[(2-aminoiminomethyl-ethyl)morphinan (44 mg, 0.09 mmol) was dissolved in a mixture of acetonitrile and tetrahydrofuran (2.5 mL/0.25 mL) and the solution was cooled in an ice bath. To this 0.1 mL of 40% HF was added dropwise, and the mixture was stirred for 2 h at room temperature. The white precipitate formed was filtered and

washed with acetonotrile to give KRS-2-63 as the fluoride salt (yield = 34 mg, 96%).

Example 21 N-(aminoiminomethylaminopropyl)-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethanotetrahydronororipavine (KRS-4-8)

(a) Preparation of N-cyanoethyl-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethanotetrahydronororipavine

7α-(1-Hydroxy-1-methylethyl)-6,14-*endo*-ethanotetrahydronororipavine was prepared according to the method of Lewis (J.W. Lewis: Narcotic Antagonists, in Advances in Biochemical Psychopharmacology, Vol. 8 edited by M.C. Braude, L.S. Harris, E.L. May, J.P. Smith and J.E.Villarreal. Raven Press, New York 1974). This compound was reacted with acrylonitrile in absolute ethanol as described. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane in 1:1 ratio as the eluent.

(b) Preparation of 3-(t-butyldimethylsiloxy)-N-cyanoethyl-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethanotetrahydro-nororipavine

N-cyanoethyl-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethanotetrahydronororipavine was reacted with t-butyldimethylsilylchloride as described for KRS-3-56. The crude product was purified by column chromatography on silica gel, using ethylacetate/hexane in 2:1 ratio as the eluent.

c) Preparation of 3-(t-butyldimethylsiloxy)-N-aminopropyl-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethanotetrahydro-nororipavine

3-(t-butyldimethylsiloxy)-N-cyanoethyl-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethanotetrahydro-nororipavine (0.11 g, 0.204 mmol) in dry ethyl ether (2 ml) was added dropwise to a suspension of lithium aluminum hydride (0.093 g, 2.45 mmol) in dry ethyl ether (2 ml).

After stirring for 3 h at room temperature, wet ether (5 ml) followed by 10% sodium hydroxide (1 ml) was added to the reaction mixture. The solution was filtered, and the white precipitate was washed with ether. The filtrate was evaporated under reduced pressure to give the amine as a clear liquid (70 mg, 63%).

d) Preparation of 3-(t-butyldimethylsiloxy)-N-(aminoimino-methylaminopropyl)-7α-(1-hydroxy-1-methylethyl)-6,14-endo-ethanotetrahydronororipavine

Anhydrous dimethylformamide (0.5 ml) was added to a mixture of 3-(t-butyldimethylsiloxy)-N-aminopropyl-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethanotetrahydro-nororipavine (70 mg, 0.129 mmol), diisopropylethylamine (0.022 ml, 0.129 mmol) and 1H-pyrazole-1-carboxamidine hydrochloride (0.019 g, 0.129 mmol), and the reaction mixture was stirred overnight at room temperature under nitrogen. The solvents were evaporated under reduced pressure, and the crude product was chromatographed on silica gel (yield = 57 mg, 76%).

e) Preparation of N-(aminoiminomethylaminopropyl)-7α-(1-hydroxy-methylethyl)-6,14-endo-ethanotetrahydronororipavine (KRS-4-8)

40% HF (0.2 ml, 0.004 mol) was added dropwise to 3-(t-butyldimethylsiloxy)-N-(aminoiminomethylaminopropyl)-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethanotetrahydro-nororipavine (57 mg, 0.097 mmol) in a 10:1 mixture of acetonitrile/tetrahydrofuran (10 ml), and the reaction mixture was stirred overnight at room temperature. The white precipitate formed was filtered, and was washed with acetonitrile and then with methanol to give KRS-4-8 as the fluoride salt (44 mg, 96% yield).

Example 22 Synthesis of (5α,6α)-7,8-didehydro-4,5-epoxy-17-(N-aminoiminomethylaminopropyl)morphinan-3,6-diol (KRS-2-47)

Preparation of 3,6-bis(t-butyldimethylsiloxy)-7,8-didehydro-4,5-epoxy-17-aminopropylmorphinan

A solution of 3,6-bis(t-butyldimethylsiloxy)-7,8-didehydro-4,5-epoxy-17-cyanoethylmorphinan (200 mg, 0.36 mmol) in dry ethyl ether (5 ml) was added dropwise to a suspension of lithium aluminum hydride (0.13 g, 3.6 mmol) in dry ethyl ether (5 ml). After stirring for 3 h at room temperature the reaction mixture was added wet ether followed by 10% sodium hydroxide (1.5 ml). The solution was filtered, and the white precipitate was washed with ether. The ether layer was evaporated under reduced pressure to give the amine as a clear liquid (yield = 0.2 g, 99%).

Preparation of 3,6-bis(t-butyldimethylsiloxy)-7,8-didehydro-4,5-epoxy-17-(N-aminoiminomethylaminopropyl)-morphinan

Anhydrous dimethylformamide (2 ml) was added to a mixture of 3,6-bis(t-butyldimethylsiloxy)-7,8-didehydro-4,5-epoxy-17-aminopropylmorphinan (0.2 g, 0.359 mmol), diisopropylethylamine (0.07 ml, 0.39 mmol), and 1H-pyrazole-1-carboxamidine hydrochloride (0.06g, 0.39 mmol) and the reaction mixture was stirred overnight at room temperature under nitrogen. The reaction mixture was evaporated to dryness under reduced pressure, and the crude product was chromatographed on silica gel (yield = 0.155 g, 72%).

Preparation of (5α,6α)-7,8-didehydro-4,5-epoxy-17-(N-aminoiminomethylaminopropyl)morphinan-3,6-diol (KRS-2-47)

3,6-bis(t-butyldimethylsiloxy)-7,8-didehydro-4,5-epoxy-17-(N-aminoiminomethyl-aminopropyl)morphinan was deprotected using 40% HF in a 10:1 mixture of acetonitrile and tetrahydrofuran as described before. The precipitate

was filtered and washed with acetonitrile, methylenechloride followed by methanol. KRS-2-47 was obtained as a white powder in 73% yield (70 mg).

Example 23 Analgesic Activity

We have found evidence that these compounds have analgesic activity by showing stereoselectivity for peripheral opioid receptors. Thus, low subcutaneous or intraperitoneal doses of N-methylnalorphninium iodide (10-300 µg/kg) showed analgesic activity in the mouse test of Hendershot and Forsaith (J. Pharmacol. Exp. Ther., 1959 125 237-240) and in the rat inflamed paw test of Randall and Selitto (Archs. Int. Pharmacodyn. Ther., 1957 111 409-419), whereas N-allylmorphinium iodide given in doses of 10 mg/kg was found to be inactive in both tests. S-methyllisothiocarbamoyl norheroin iodide was also active in both tests after administration of doses of 1-3 mg/kg.

Compound KRS-41 (Example 16) was tested for analgesic activity in two mouse analgesia models. In the first test, the test substance was administered to groups of 5 ICR derived male mice weighing 22 ± 2 g one hour before subplantar injection of formalin (0.02 ml, 1% solution). Reduction of the induced hind paw licking time recorded during the following 20 to 30 minute period by 50% or more indicates analgesic activity. Table 2 below shows that KRS-41 has analgesic activity at 3 times the morphine concentration, which is consistent with the relative opiate receptor activities discussed below in Example 23.

Table 2

Treatment	% Reduction in Hind Paw Licking time
Vehicle (5% DMSO/saline)	0
Morphine HCl (10 mg/kg)	100
KRS-41 (10 mg/kg)	12
KRS-41 (30 mg/kg)	75

In the second test, the test substance was administered to groups of 3 ICR derived male mice weighing 22 ± 2 g 30 minutes before injection of PQ (2 mg/kg). Reduction in the number of writhes by 50% or more per group of animals observed during the 5 to 10 minute period after PQ administration, relative to a vehicle treated control group, indicates analgesic activity. Table 3 below shows that KRS-41 has analgesic activity at 5 times the morphine concentration.

Table 3

Treatment	% Reduction in Writhes
Vehicle (5% DMSO/saline)	0
Morphine HCl (3 mg/kg)	87, 73 (two tests)
KRS-41 (3 mg/kg)	18
KRS-41 (15 mg/kg)	93

Example 24 Guinea Pig Stimulated Ileum Preparation

Five compounds, KRS-41 (Example 16), KRS-2-19 (Example 12), KRS-3-28 (Example 18), KRS-3-30-2 (Example 20) and KRS 3-56 (Example 21) were tested for opiate activity in a standard guinea-pig stimulated ileum assay, using morphine as a standard.

Male Monash strain guinea-pigs were killed and the ileum removed. Segments (approxm. 1.5-2.5 cm) were

mounted on tissue holders with in-built stimulating electrodes, and set up in 5 ml isolated organ baths containing Krebs solution of the following composition (mM): NaCl 118.4; KCl 4.1; $MgSO_4.7H_2O$ 1.2; KH_2PO_4 1.2; $NaHCO_3$ 25; glucose 11.1; $CaCl_2.2H_2O$ 2.5. The Krebs solution was bubbled with carbogen (95% O_2, 5% CO_2), and the preparations maintained at 37°C under 1 gram resting tension. The tissues were stimulated transmurally using single pulses of 0.5 ms duration at 0.2 Hz and 40 V from a Grass SD9 stimulator, and allowed to equilibrate under these conditions before the addition of drugs.

Cumulative dose-response curves to morphine (using increments of a half log unit) were obtained before obtaining cumulative dose-response curves to the test compounds. The results are shown in Figure 1.

Surprisingly, KRS-41 showed excellent activity compared to morphine (Figure 1b). This compound has an aminoiminoethyl substituent on the tertiary N atom, and was expected to have either no activity or antagonist activity. KRS-4-8 gave results similar to those observed with buprenorphine.KRS 3-56 (Figure 10) also showed even more striking activity, with a potency of approximately 6 times that of morphine, and was a full agonist of the μ opiate receptor. KRS-2-47 is expected to give similar results.

Although KRS-3-28 had low potency compared to morphine, its activity in this assay is comparable to that of codeine. Codeine is metabolized *in vivo* to morphine, so its effect after oral administration is comparable to that of morphine given by injection. KRS-3-28 is expected to metabolize in similar fashion after oral administration or parenteral injection to give a buprenorphine-like compound.

In contrast, KRS-2-19 (Figure 16) and KRS-3-30-2 (Figure 1a) showed only partial morphine agonist activity. It therefore appears that a spacer group in which n is 2 results in stronger opiate activity than a spacer in which n is 1.

KRS-2-63 showed partial agonist activity, but would be expected to be converted *in vivo* by demethylase enzymes in the liver to KRS-41, in a similar manner to metabolism of codeine. Similar results would be expected for other compounds of the invention with a methoxy group at carbon 3.

Example 25 Effect of KRS 3-56 and KRS-41 on the Central Nervous System

The effects of compounds KRS-3-36 and KRS-41 on the central nervous system were compared with that of morphine using a standard Irwin test (Irwin, S.; Psychopharmacologic (Berlin), 1968 13 222-257). The relevant results are shown in Tables 4 and 5.

Table 4

Test	Vehicle	Morphine 10 mg/kg
Tail elevation	2.5 ± 0.7	7.0 ± 0.7
Respiratory rate	5.6 ± 0.2	4.1 ± 0.3
Positional Passivity	4.7 ± 0.3	8.7 ± 0.4
Grip strength	5.1 ± 0.4	3.7 ± 0.3
Corneal reflex	4.5 ± 0.2	2.9 ± 0.2

Table 5

Test	Vehicle	KRS-41 30 mg/kg	KRS-3-56 3 mg/kg
Tail elevation	4.4 ± 0.2	2.0 ± 0.4	2.4 ± 0.4
Respiratory rate	5.1 ± 0.2	5.1 ± 0.2	5.4 ± 0.2
Positional Passivity	4.7 ± 0.2	4.7 ± 0.3	5.4 ± 0.5
Grip strength	5.0 ± 0.3	5.1 ± 0.4	5.1 ± 0.2
Corneal reflex	4.9 ± 0.1	4.9 ± 0.1	4.8 ± 0.1

These results indicate that the compounds of the invention, while retaining the analgesic activity of morphine, are non-sedating and do not cause respiratory depression. It is believed that this results from exclusion of the compounds from the central nervous system.

It will be apparent to the person skilled in the art that while the invention has been described in some detail for the purposes of clarity and understanding, various modifications and alterations to the embodiments and methods described herein may be made without departing from the scope of the inventive concept disclosed in this specification.

CLAIMS:

1. An opioid compound of general formula I

[opioid-N]-[spacer]-[charged group],

I

in which an opioid compound is linked via the nitrogen at position 17 to a spacer group, which in turn is linked to a charged group,

or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, in which the spacer is a straight or branched alkyl, alkenyl or alkenyl chain of 1 to 6 carbon atoms, which may optionally be substituted.

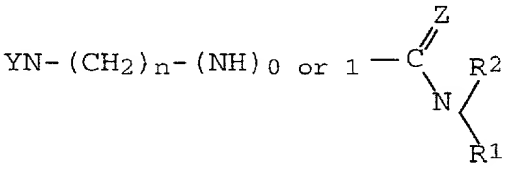
3. A compound according to Claim 1, in which the spacer is a cyclic alkyl, alkenyl or alkynyl group, which may optionally be substituted.

4. A compound according to any one of Claims 1 to 3, in which the spacer group is unsubstituted.

5. A compound according to any one of Claims 1 to 4, in which the spacer group is of 2 to 3 carbon atoms.

6. A compound according to any one of Claims 1 to 5, in which the charged group is an amidine or guanidine group.

7. A compound according to Claim 1, of general formula (II)



in which

YN- represents an organic residue obtained by removal of the R group from an opioid compound of general formula

YN-R

(IIIa)

wherein R is H, alkyl of 1 to 6 carbon atoms, or cyclopropylmethyl,

or of the general formula

$$Y^1\text{-}N(R^4)\text{-}R$$

(IIIb)

wherein R^4 is methyl or ethyl, and

Y^1-NR^4 represents the corresponding organic residue;

Z is O, S or NR^3;

R^1 is H_1, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

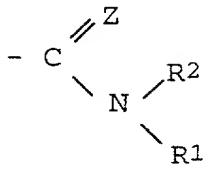
R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;

n is an integer of 1 to 6,

and wherein

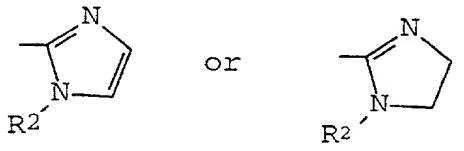
R^1 and R^3 may together complete an addition ring, or a pharmaceutically acceptable salt thereof.

8. A compound according to Claim 7, in which R^1 and R^3 together complete an addition ring, and the grouping



forms a heterocyclic moiety.

9. A compound according to Claim 8, in which the heterocyclic moiety is a 2-imidazolyl or 2-imidazolinyl group of formula:



10. A compound according to Claim 8 or Claim 9, in which R is CH_3.

11. A compound according to any one of Claims 8 to 10, in which n is 2 or 3.

12. A compound according to any one of Claims 8 to 11, in which Z is NH, and R^1 and R^2 are both H.

13. A compound according to any one of Claims 8 to 11, in which the precursor of YN- or Y^1NR^4- is a compound selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, etorphine, acetorphine, ketobemidone, ethoheptazine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine and metazocine.

14. A compound according to Claim 13, in which the precursor of YN- or Y^1NR^4- is morphine, codeine or buprenorphine.

15. A compound according to Claim 1, in which the opioid compound of formula (IIIa) or (IIIc) is selected from the group set out in Table 1.

16. A compound according to Claim 1, in which the compound of general formula I is selected from the group consisting of KRS-41, KRS-2-19, KRS-3-7, KRS-3-23-4, KRS-3-28, KRS-3-30-2, KRS-3-56, KRS-2-63, KRS-4-8, and KRS-2-47, as herein defined.

17. An opiate receptor agonist having analgesic properties and having reduced or no CNS activity, of general formula I or general formula II as defined in any one of claims 1 to 16.

18. A method of reducing the central nervous system activity of an opioid compound, comprising the step of linking the nitrogen atom at position 17 of said compound to a spacer group, which in turn is linked to a charged group, optionally via a spacer group.

19. A method for the preparation of a compound of formula II as defined in any one of Claims 8 to 14, in which YN- may be replaced by Y^1NR^4-, comprising the steps of

(a) Reaction of a compound of formula

YN-H

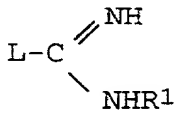
(IV)

with a cyanamide, R^1NHCN, according to the equation

$$YN\text{-}H + R^1NHCN \rightarrow YN\text{-}C(=NH)\text{-}NHR^1$$

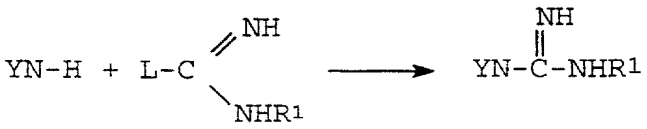
or

(b) Reaction of a compound of formula (IV) with a compound of formula



(V)

wherein L is a leaving group, according to the equation



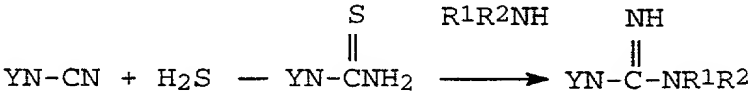
20. A method for the preparation of a compound of formula II as defined in any one of Claims 8 to 14 in which Z is NR^2, comprising the steps of

(a) Reaction of a compound of the formula

YN-CN

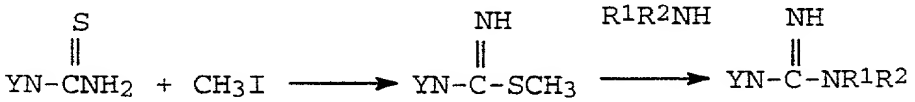
(VI)

with H_2S to obtain an N-thiocarboxamide YN-$CSNH_2$, which is reacted with an amine R^1R^2NH according to the two-stage equation



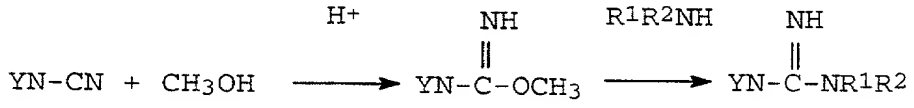
to yield compounds of the invention where Z is S and where Z is NH, or

(b) Methylating the N-thiocarboxamide to yield an isothiourea compound, which is in turn reacted with an amine R^1R^2NH:

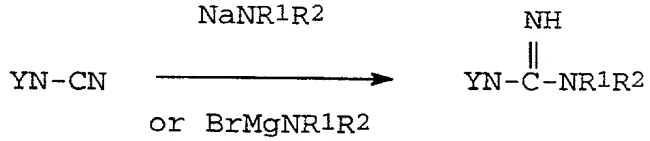


21. A method of synthesis of a compounds of formula (II) as defined in any one of Claims 8 to 14, comprising the step of reacting an N-cyano compound of

formula (VI) as defined in Claim 19 with methanol under acidic conditions to yield an isourea, which in turn is reacted with an amine according to the equation



22. A method of synthesis of a compound of formula (II) as defined in any one of Claims 8 to 13 in which Z is N, comprising the step of reacting an N-cyano compound of formula (VI) as defined in Claim 19, and a metallated residue



23. A composition comprising a compound according to any one of Claims 1 to 16, together with a pharmaceutically acceptable carrier.

24. A method of inducing analgesia, comprising the step of administering an effective amount of a compound according to any one of Claims 1 to 16 to a mammal in need of such treatment.

25. A method according to Claim 23 in which the mammal is a human.

26. Use of a compound according to any one of Claims 1 to 16 in medicine.

27. Use of a compound according to any one of Claims 1 to 16 for the manufacture of a medicament for inducing analgesia.

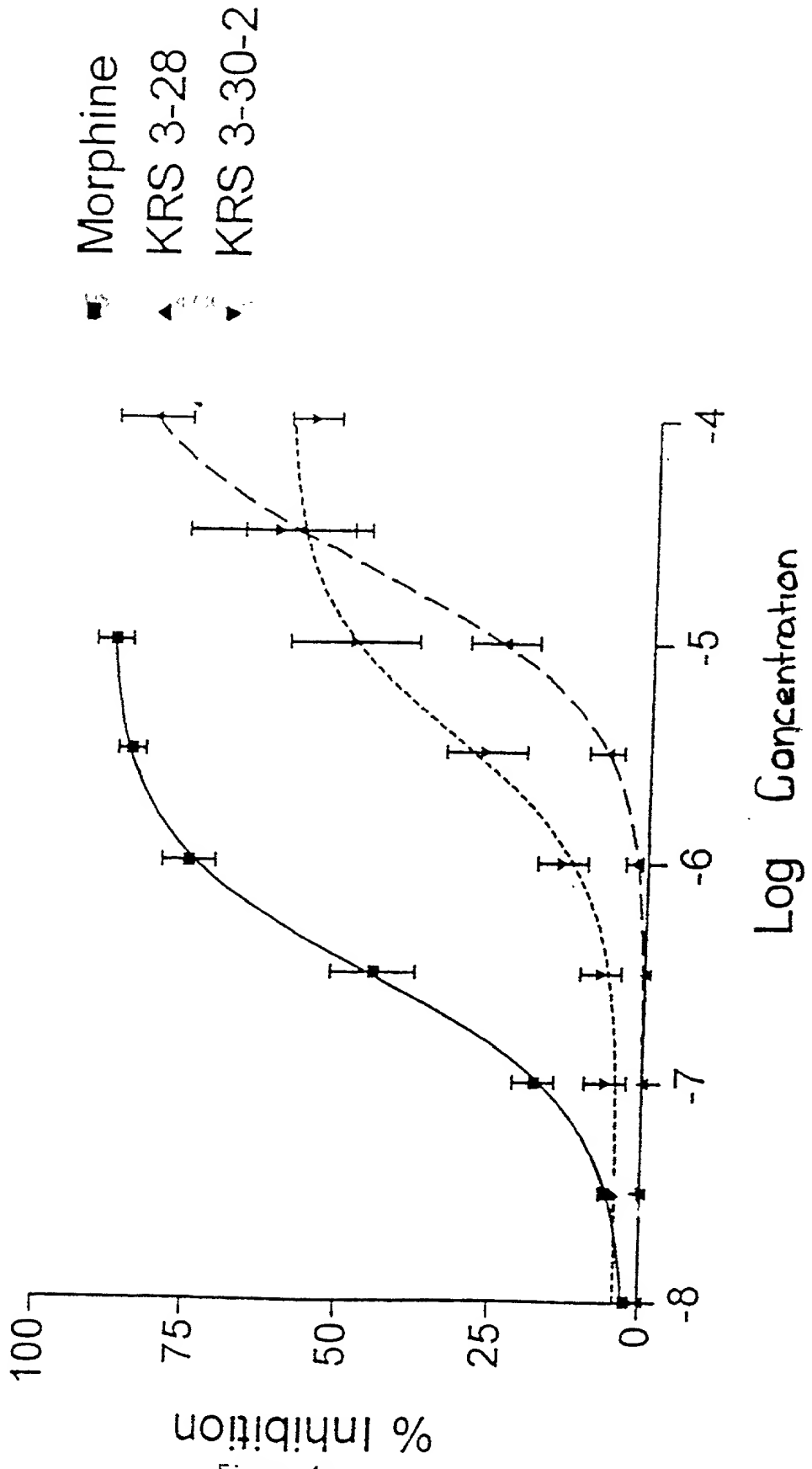

Morphine
KRS 3-28
KRS 3-30-2
% Inhibition
100
75
50
25
0
-8
-7
-6
-5
-4
Log Concentration

Figure 1a

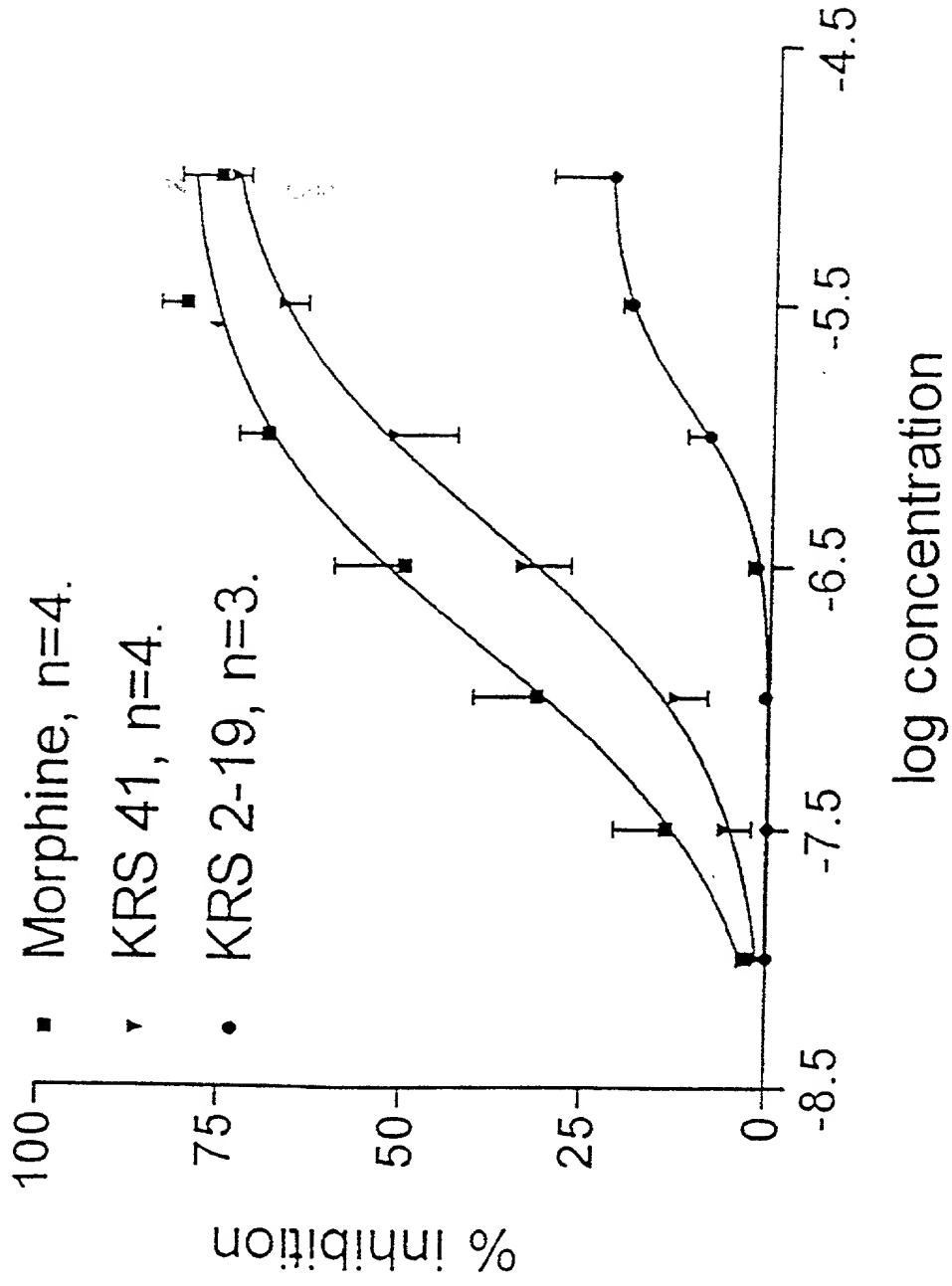

Morphine, n=4.
KRS 41, n=4.
KRS 2-19, n=3.
% inhibition
100
75
50
25
0
-8.5
-7.5
-6.5
-5.5
-4.5
log concentration

Figure 1b

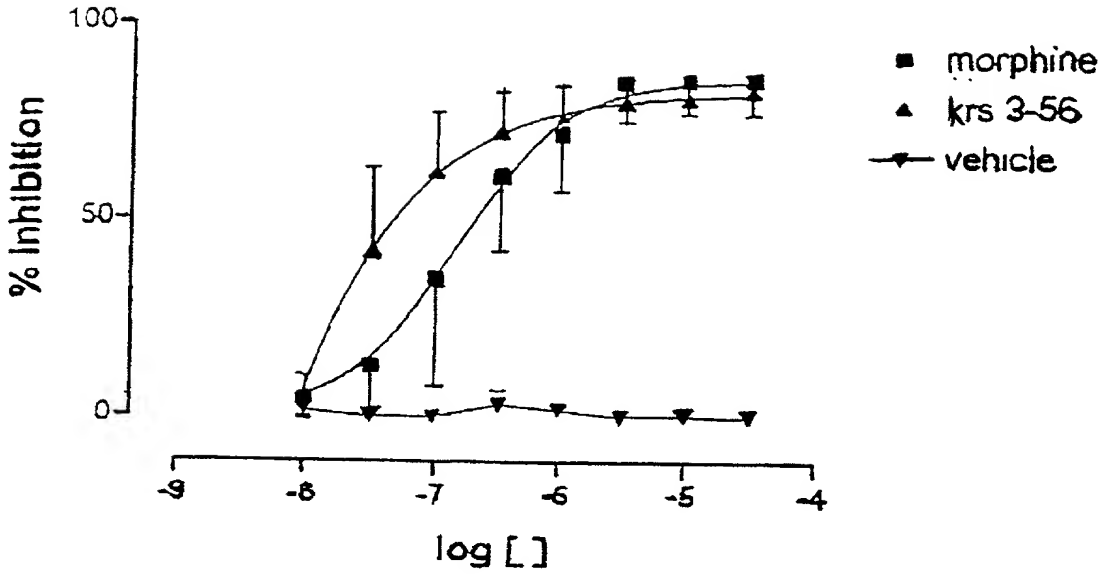


Figure 1c

PATENT
ATTORNEY DOCKET NO: 50124/005001

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled THERAPEUTIC COMPOUNDS, the specification of which

- ☐ is attached hereto.
- ■ was filed on June 21, 2000 as Application Serial No. 09/582,059 and was amended on _____.
- ☐ was described and claimed in PCT International Application No. _____ filed on _____ and as amended under PCT Article 19 on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56(a).

FOREIGN PRIORITY RIGHTS: I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

Country	Serial Number	Filing Date	Priority Claimed?
PCT	PCT/AU99/00062	29 January 1999	Yes

PROVISIONAL PRIORITY RIGHTS: I hereby claim priority benefits under Title 35, United States Code, §119(e) and §120 of any United States provisional patent application(s) listed below filed by an inventor or inventors on the same subject matter as the present application and having a filing date before that of the application(s) of which priority is claimed:

Serial Number	Filing Date	Status

COMBINED DECLARATION AND POWER OF ATTORNEY

NON-PROVISIONAL PRIORITY RIGHTS: I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information I know to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Serial Number	Filing Date	Status

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Paul T. Clark, Reg. No. 30,162, Karen L. Elbing, Ph.D. Reg. No. 35,238, Kristina Bieker-Brady, Ph.D. Reg. No. 39,109, Susan M. Michaud, Ph.D. Reg. No. 42,885, Mary Rose Scozzafava, Ph.D., Reg. No.36,268, James D. DeCamp, Ph.D., Reg. No. 43,580, Sean J. Edman, Reg. No. 42,506.

Address all telephone calls to: Paul T. Clark at 617/428-0200.

Address all correspondence to: Paul T. Clark at Clark & Elbing LLP, 176 Federal Street, Boston, MA 02110.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Full Name (First, Middle, Last)	Residence Address (City, State, Country)	Post Office Address (Street, City, State, Country)	Citizenship
Roy W. Jackson	Burwood, Victoria 3125 AUSTRALIA AU	30 Through Road Burwood, Victoria 3125 AUSTRALIA	AU
Signature: W. Roy Jackson			Date: 9/10/'00

COMBINED DECLARATION AND POWER OF ATTORNEY

Full Name (First, Middle, Last)	Residence Address (City, State, Country)	Post Office Address (Street, City, State, Country)	Citizenship
20 Kamani R. Subasinghe	Glen Waverley, Victoria 3150 AUSTRALIA AU	11 Ilora Court Glen Waverley, Victoria 3150 AUSTRALIA	AU
Signature: K Subasinghe			Date: 9/10/00

Full Name (First, Middle, Last)	Residence Address (City, State, Country)	Post Office Address (Street, City, State, Country)	Citizenship
30 Alan L. A. Boura	Clayton, Victoria 3168 AUSTRALIA AUX	c/o Monash University Dept. of Pharmacology Wellington Road Clayton, Victoria 3168 AUSTRALIA	AU
Signature: A. Boura			Date: 16/10/00